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Executive Assistant
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FACSIMILE TRANSMITTAL SHEET

TO: Josh McLaughlin	FROM: Angelica Diega
COMPANY: Burnham Institute	DATE: 4/30/03
FAX NUMBER: 858-646-3189	
PHONE NUMBER:	TOTAL NO. OF PAGES INCLUDING COVER: 13
RE: Dr. Arap's CaP CURE Research Award Proposal	

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NOTES/COMMENTS:

As requested...

EXHIBIT 1

1198CA

CaP CURE Award Application Face Sheet

1. Name/Principal Investigator(s) — First: Wadih; Middle Initial: ; Last: Arap; Degree(s): M.D., Ph.D.

2. Title: Senior Research Associate; Position:

3. Institution Name: The Burnham Institute

Department:

4. Dr. Erkki Ruoslahti's Laboratory. Cell Adhesion Program.

Complete Mailing Address: 10901 North Torrey Pines Road

City: La Jolla; State: CA; Zip Code: 92037; Country: USA

5. Telephone (Area Code): (619)455-6480 x3201; Facsimile (Area Code): (619)646-3199; E-Mail: warap@burnham-inst.org

6. Co-Investigator(s) – include degree(s):

7. Proposal Title: "MEDICAL PROSTATECTOMY BY VASCULAR-TARGETED CELL DEATH INDUCTION."

8. Please place a 50-100 word, typewritten abstract here. It should summarize your proposed research.

We isolated of a panel of peptides that bind selectively to prostate vasculature. This was accomplished by using *in vivo* screening of peptide libraries in mice. In as yet unpublished work, we have used these prostate-homing peptides to deliver a pro-apoptotic peptide to prostate blood vessels. Within 24 hours of intravenous administration, a single dose of this prostate-targeted compound induced a selective, massive cell death in the prostatic parenchyma. In contrast, examination of several other organs showed only minor changes. Encouraged by these promising results, we propose to evaluate this "targeted medical prostatectomy" in a prostate cancer transgenic mouse model. We expect that the reduction of prostate tissue made possible by our procedure will allow an early eradication of pre-malignant and malignant lesions, thus reducing the incidence of prostate cancer in the mice. This procedure may eventually provide a non-invasive alternative to surgical treatment in patients.

9. Circle the amount of funding requested from CaP CURE: $50,000 $75,000 (**$100,000**) $150,000 $200,000 Other_____

10. Please identify other sources currently funding your work:

CaP CURE, TRDRP of the University of California, Department of Defense.

11. Circle the (one) best category for your proposed research:

Clinical (Human) Androgen Receptor Angiogenesis Apoptosis Bone Genomics Molecular Biology Molecular Genetics Nutritional Retinoid/VIT D Alternative Medicine (**Experimental Therapeutics**) Other_____

12. How did you hear about this competitive award (circle best answer)? Colleague _____ (Name) Journal _____ (Name) Meeting _____ (Organization) Other CaP CURE award recipient.

A. INTRODUCTION

The specific delivery of drug therapy has been a long standing goal of medicine. If it were possible to deliver drugs selectively to their intended target organs, many drugs that are effective, but too toxic, could now be used. For example, systemic treatment of tumors relies largely on cytotoxic chemotherapy and the currently used chemotherapeutic drugs have the narrowest therapeutic indices. Thus, cancer treatment could benefit enormously from technology allowing selective delivery of cytotoxics; higher concentrations of the agent would be reached in the tumor, and fewer side effects would result. Unfortunately, there are only a few situations in which targeted drug delivery is possible: Intra-arterial injection is too invasive; monoclonal antibodies against tumor antigens have been used but specificity and poor tumor penetration tend to limit their efficacy (1, 2).

There are many indications that vascular beds in different organs and tissues differ from one another, and that such differences serve cellular trafficking functions (14, 18). Thus, lymphocyte-homing to lymphoid tissues and sites of inflammation is guided by specific address molecules in the vascular endothelium (14). To some degree, site-specific tumor metastasis also depends on vascular addresses; it is clear that prostate cancer cells show preferences in vivo that are not explained by circulatory routing (18). The distribution of prostate cancer metastasis seems to depend on the binding of circulating tumor cells to endothelial receptors in sites such as the bone marrow.

Our group has developed a novel approach to study organ-selective vascular markers, and have documented an unprecedented degree of heterogeneity in the vasculature of various organs (13, 14) and tumors (2, 12). The method is based on selection of large phage display peptide libraries (16) in vivo (2, 11-14). Primarily, endothelial cell receptors with tissue-specific differential expression (11, 13, 14) and angiogenic cell markers in tumors (1-3, 12) are targeted. Unlike the earlier antibody work, the phage library screening directly selects for molecules capable of homing to a target tissue in vivo without any preconceived notion about the receptor. Peptides that home to the vasculature in the brain, kidney, lung, pancreas, uterus, skin, and retina (13, 14), and tumors (2, 12) have been reported. We have already identified the receptor for a class of tumor-targeting peptides as α_v integrins (2, 11, 12); moreover, CD13/aminopeptidase N (unpublished data) and the membrane proteoglycan NG2 (ref. 3) are strong candidate receptors for two other classes of tumor-homing peptides. We have also shown that tumor-targeting peptides can be used for selective delivery of drugs to tumor vasculature (2). In work in progress, we uncovered novel tissue-specific receptors in the vasculature of normal organs and angiogenic endothelial cell markers in the vasculature of tumors (unpublished data), providing new insights to the specificity of vascular endothelium. Finally, we have targeted the blood vessels of several additional organs including the prostate. Thus, the prostate, like all of the other tissues we have examined so far, puts a specific molecular signature on its vasculature that can be detected with our in vivo phage display method. Recent evidence has suggested that prostate size is controlled by vascular endothelial cells (5). As shown in the Preliminary Results section, the high specificity conferred by the prostate vasculature-targeting peptides has allowed us to direct pro-apoptotic moieties selectively to prostate blood vessels. These targeted pro-apoptotic peptides promote a selective and marked ablation of prostate mass. We hope that the reduction in the prostate tissue caused by massive apoptosis will allow an early elimination of pre-cancerous and cancerous lesions and perhaps lead to a reduction in the risk of overt cancer development. If our expectations are realized, these targeted compounds will become useful agents against prostate cancer and may provide a medical alternative to reductive surgery.

B. SPECIFIC AIMS

We propose to synthesize pro-apoptotic peptides targeted to the vasculature of the prostate and to evaluate selected compounds in a prostate cancer transgenic animal model.

C. PRELIMINARY RESULTS

Targeting the prostate vasculature. To select peptides that home to a given organ, phage are injected IV, rescued from the target organ by a host bacteria, amplified in vitro, and re-injected to obtain further enrichment. After three rounds of selection, bulk phage preparations are usually obtained that accumulate in the target organ several fold more than in control organs. The phage confers resistance to a selectable marker (e.g., tetracycline) to the host bacteria. This allows counting the number of phage in tissues after administration of an individual homing and a control phage as one estimate of the selectivity of the homing peptides. Figure 1 shows an example of in vivo prostate targeting.

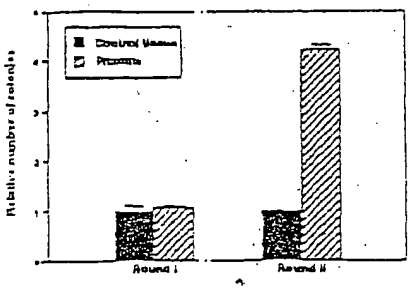


Fig. 1. Prostate targeting. Intravenous injection of a phage library displaying random 7-residue peptides (X_7 library) in mice followed by rescue of the phage pooled from the prostate yielded > 4-fold enrichment of the phage in the prostate relative to other control organs after only 2 rounds of selection. Brain has been used as one of the controls.

The peptide sequences recovered are shown in Table 1.

Table 1: Prostate-homing phage characterization

Sequence	Library	Clones	Round	Screening*	Prostate/Ctrl
SMSIARL	X_1[1]	3/18 (17%)	II	Conventional	94
VSFLEYR	X_1	2/18 (11%)	II, III	Conventional	17
VMGVIA	X_1	3/18 (17%)	II	Non-amplification	ND
RAGYAA	X_1	3/18 (17%)	II	Non-amplification	ND
SVRHRE	X_1	2/18 (11%)	II	Non-amplification	ND

(*) Conventional or non-amplification; (1) Any amino acid

Thus far, our strongest prostate-homing peptide displays the peptide SMSIARL; its homing ability is shown in Fig. 2.

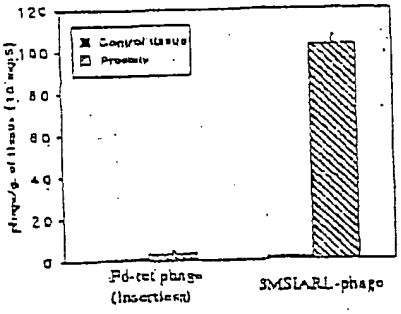


Fig. 2. SMSIARL peptide homes specifically to prostate. Phage displaying an SMSIARL peptide or insertless control phage (Fdtet) were injected intravenously in mice under anesthesia. After 5 minutes, the animals were euthanized and phage were recovered and quantified by tetracycline-resistant colony counting. On average, SMSIARL-phage showed a 25- to 35-fold enrichment over control organs (brain shown).

As another test of specificity, and to examine the localization of the homing peptides in the prostate, we detected the injected phage in tissues by immunoperoxidase staining for phage proteins. Immunostaining results confirmed the specificity of homing and show that our peptides homed into the prostate (Fig. 3). These data strongly suggests that internalization of the phage displaying the SMSIARL peptide occurs. Other examples of peptide-driven phage internalization have been reported (7).

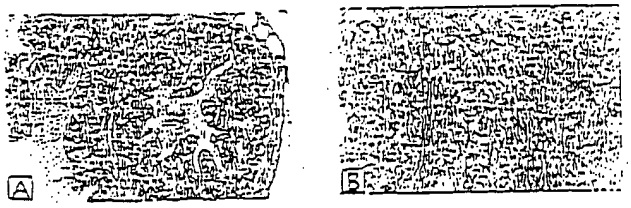
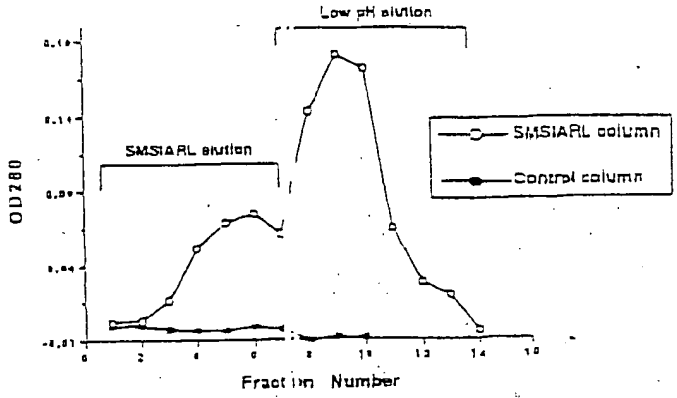


Figure 3. Immunohistochemical staining of phage in the mouse prostate after intravenous injection. SMSIARL-phage (left panel) and insertless control phage (right panel) were injected intravenously into mice. Phage were allowed to circulate for 24 hours. Prostate and control organs were removed, fixed in Bouin's solution, embedded in paraffin and tissue sections were prepared. An antibody against M-13 phage (Pharmacia) was used for the staining. Magnification: 200x. Control organs are not shown but they were negative except for liver and spleen. The reason for that is that circulating phage is non-specifically trapped by the reticuloendothelial system (2, 11-14); mice injected with control phage also showed hepatic and splenic immunostaining (data not shown).

Isolation of a receptor for the prostate-homing peptide. We have made progress in identifying a receptor for SMSIARL, one of our prostate-homing peptides. Prostate extract fractionated on SMSIARL-Sepharose yields a specific profile upon the competate peptide elution and specific bands at 85 kDa and 60 kD! (Fig. 4). We are currently scaling up the affinity chromatography such that enough protein for mass spectrometry, microsequencing, and antibody preparation can be obtained



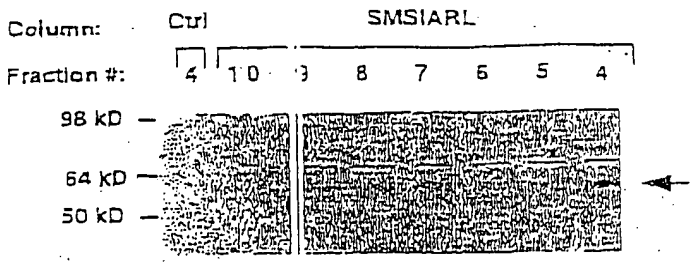


Fig. 4. Elution profile and SDS gel analysis of proteins isolated on Sepharose-coupled prostate homing peptide. Octylglucoside extract of mouse prostates were fractionated on SMSIARL-Sepharose. The columns were washed with buffer and the bound proteins eluted with a solution of the same peptide as in the column. Prostate extracts fractionated on the prostate homing peptide column. Lanes 4-7 are successive fractions eluted with the SMSIARL peptide after extensive washing of the resin with buffer. Elution profile (upper panel) and SDS gel analysis followed by silver staining (lower panel) are shown. The appearance and elution position of the two main bands suggest that the 85 kDa band may be an intracellular protein (sharp band, early elution) and that the 60 kDa band is a better candidate for a specifically bound cell surface SMSIARL receptor (broad band suggesting glycosylation, late elution). The 60 kDa protein is marked by an arrow; MW markers are shown.

Choice of cytotoxic moieties and induction of a targeted "medical prostatectomy." We have selected three types of cytotoxic moieties that are potential candidates for targeted delivery to the prostate vasculature: Anti-mitochondrial peptides (8), the ricin-A chain (17), and a novel class of synthetic pro-apoptotic peptides (15). Studies with these targeted compounds are in different stages of development in our laboratory.

The results presented here as a proof-of-principle were obtained with an anti-mitochondrial motif (8) used as the cytotoxic moiety. However, because some general toxicity was observed this agent, we will also evaluate additional classes of cytoxic peptides and proteins in order to select an optimal compound for the prostate targeting.

(i) Targeting of anti-mitochondrial peptides: The membranes of prokaryotic bacteria and eukaryotic cell mitochondria have similar properties. Both membranes have a negatively charged outer membranes. Thus, anti-bacterial peptides which interfere with membrane potential are often anti-mitochondrial peptides as well. A series of synthetic amphipathic peptides with shared anti-bacterial and anti-mitochondrial properties have been reported (8). In collaboration with Dr. Dale Bredesen's group at this Institute, we utilized the motif $(KLAKLAK)_2$, an anti-mitochondrial peptide, as the prototype of this class to be targeted by our prostate-homing peptides to the prostatic blood vessels.

We treated male CD-1 mice with the prostate-targeted compound SMSIARLKLAKLAKKLAKLAK. As controls, we used either $(KLAKLAK)_2$ conjugated to the control peptide CARAC (data presented below) or a mixture of unconjugated $(KLAKLAK)_2$ plus SMSIARL (similar results, data not shown). A single dose of 200 μg of targeted peptide was used. We analyzed the prostate macro and microscopically at 24 and 48 hours posttreatment. We observed a striking reduction in the size and change in morphology of the prostate while the other organs appeared intact. Histopathology confirmed that the prostate, but not other tissues, has been affected by marked, specific cell death induction (Figs. 5-8).

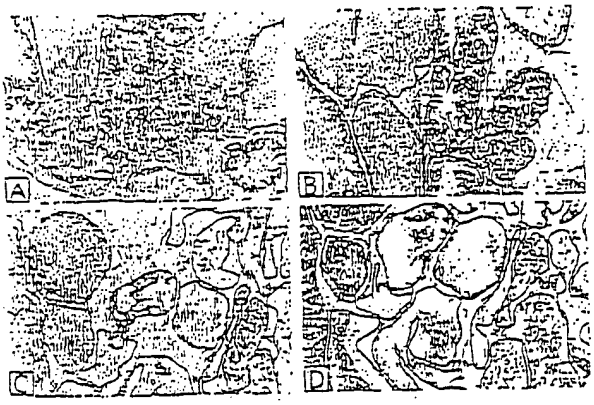


Fig. 5. Effect of treatment in the dorsolateral prostate. Prostates were fixed in Bouin's solution and sections stained (H&E, A and C; Masson' s trichrome, B and D). Mice received a single dose of a pro-apoptotic moiety conjugated to the control peptide CARAC (A and B) or to the prostate-homing peptide SMSIARL (C and D) and were killed 24 h afterwards. The most striking changes were found in the dorsolateral lobes: 80% of glands were deprived of epithelium and the remaining epithelium was markedly reduced to a discontinuous, thin layer. There were intensive shedding of the prostatic glandular epithelium into the lumen; degenerated cells floating in the gland lumen showed nuclear condensation and/or fragmentation or ballooning of the cytoplasm; increased eosinophilia; extensive spongiosis and lymphocyte infiltration.

The rodent prostate is divided into dorsal, lateral, and ventral lobes while the human prostate is divided into transitional, central, and peripheral zones. Because the rodent dorsolateral lobes are analogous to the human peripheral zone where most prostate cancers occur, we first examined the dorsolateral lobes. Of interest, the major effect of the treatment was observed in that area (Fig 5). However, pathological alterations in the ventral lobe of the prostate were noted as well (Fig. 6).

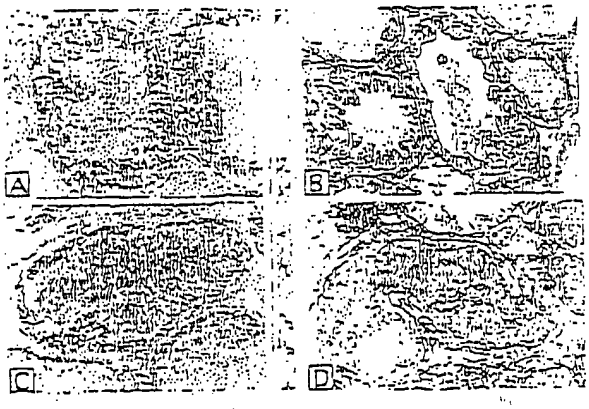


Fig. 6. Effect of treatment in the ventral prostate. Prostates were fixed in Bouin's solution and sections stained (H&E, A and C; Masson' s trichrome, B and D). Mice received a single dose of a pro-apoptotic moiety conjugated to the control peptide CARAC (A and B) or to the prostate-homing peptide SMSIARL (C and D) and were killed 24 h afterwards. Focally, in the prostate-targeted group there were losses of cell borders, and epithelial shedding in glands of ventral lobe. Nuclei were lost and the staining became more homogenously eosinophilic

In contrast, there were no major or specific pathological changes in multiple internal organs used as controls for the prostate-targeted pro-apoptotic compound (Fig. 7).

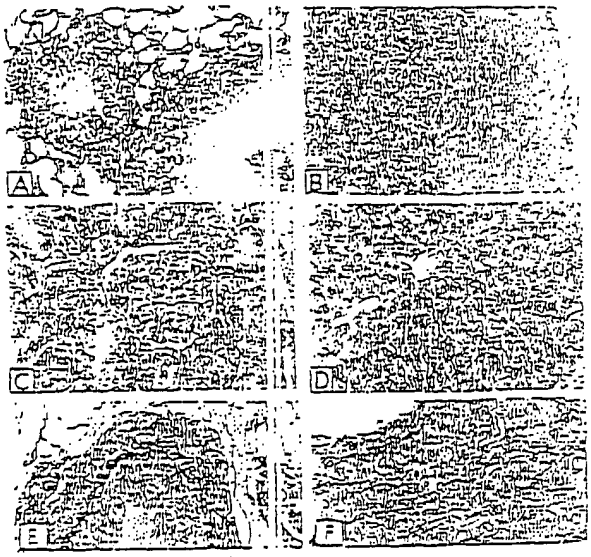


Fig. 7. Effect of treatment in control organs. Organs were fixed in Bouin's at 24 h posttreatment with a single dose of the prostate-targeted proapoptotic moiety and stained according to the Masson's trichrome method. Shown are lung and bronchi (A), brain (B), kidney (C), liver (D), urothelium (E), and a prostatic autonomic ganglion (F).

Although non-specific signs toxicity were observed in a few animals, they were usually more severe and more diffuse in the non-targeted pro-apoptotic moiety (alone or conjugated to a control peptide, data not shown). To allow for comparison, the effect of therapy in prostates of the same mice used to harvest the controls (Fig. 7) are also shown (Fig. 8).

Fig. 8. Final pathologic alterations in the prostate. Mice received either pro-apoptotic peptide-CARAC (Panels A and B) or pro-apoptotic peptide-SMSIARL (Panels C and D). Prostates from some of the same animals used for harvesting of the control organs (in Fig. 7) are shown here for comparison. Severe, terminal pathologic alterations due to prostate cell death induction are disseminated. Under these end-stage conditions, the parenchyma of the prostate has been virtually eliminated (Magnification: Panels A and C, 40x; Panels B and D, 200x).

The experiments proposed here--with this and other cytotoxic moieties--will directly determine the final value of this approach as a targeted therapy for prostate cancer in a transgenic model.

(ii) Targeting of ricin-A chain: We will also use the ricin-A chain to test the potential of the homing peptides to reduce the prostate mass. The A chain is a highly potent toxin which, when delivered intracellularly, disrupts protein synthesis. In the complete ricin molecule a B chain, which binds to cell surface receptors , delivers the A chain into the cytoplasm. The isolated A chain is relatively non-toxic, because it cannot enter a cell. The B chain can be replaced with other molecules that bind to cell surfaces, and a vast literature exists on various targeted toxins based on this principle (reviewed in 17). We will deliver the ricin-A chain into the endothelial cells of prostate blood vessels by using the homing peptides as the substitute for the B chain.

In collaboration with the group of Dr. Sjur Olsnes (Institute for Cancer Research, The Norwegian Radium Hospital, Oslo, Norway), construction and purification of ricin-A-conjugates were performed as follows: Coding sequences of the peptides SMSIARL and VSFLEYR (Table 1) were added to the C-terminal end of ricin-A-chain by PCR. A KDEL-sequence which increases the toxicity of ricin-A-chain was also included. The constructs were cloned into the expression plasmid pUTA using standard cloning techniques to yield pUTA-Prst1 and pUTA- Prst2. Cultures of *E. coli* JM101 harboring the expression plasmids pUTA-Prst1 or pUTA-prst2 were grown at 30°C. Expression of protein was induced by 0.1 mM IPTG. After 4 hours incubation at 30°C the cells were harvested by centrifugation, resuspended in 30 ml of 5 mM sodium phosphate (pH 6.5), and sonicated. The ricin-A-conjugates were purified by ion exchange chromatography using CM Sepharose CL-6B (Pharmacia). The proteins were eluted with a linear 0.1 M to 0.3 M sodium chloride gradient. Experiments in vitro suggest that the biological activity of ricin-A was not abrogated by the conjugation (data not shown). Pilot in vivo experiments are scheduled to be initiated shortly. Controls include a mixture of unconjugated ricin-A chain plus prostate targeting peptide (SMSIARL or VSFLEYR) and the ricin-A chain fused to a control peptide.

(iii) Targeting of pro-apoptotic peptides: Recently, the group of Dr. Renato Baserga has reported on a novel class of synthetic peptides of biological origin that induce apoptosis at concentrations as low as 10^{-12} - 10^{-13} M (ref. 15). Indeed, this class of peptides has the best therapeutic index of all pro-apoptotic peptides—natural or synthetic—we found described in the literature. Moreover, non-specific toxicity was ruled out because single amino acid substitutions completely abrogate their pro-apoptotic effect. Surprisingly, three peptides from this class had been previously known from the literature: YLEPGPVTA is recognized by tumor-specific human CTL lines (4), LLDGTALRL is derived from gp100 and involved in the regression of melanomas (9), and FBCNTAQPG is derived from connexin 37, and induces CTL response against lung carcinomas (10). It remains unclear whether the remarkable apoptosis-inducing ability of these peptides is related to their role in immunological phenomena. However, the fact that they are equally effective on human and murine, normal and malignant cells suggest some other interpretation. The pro-apoptotic properties of these reagents were discovered serendipitously during unrelated experiments designed to test whether these peptides could bind to the IGF-I receptor (15). Despite their as yet unknown mechanism of action, these simple, linear peptides are outstanding candidates to be targeted as cytotoxic moieties of choice.

C. EXPERIMENTAL DESIGN AND METHODS

The goal of this proposal is to develop ways of delivering agents that can reduce the mass of the prostate through induction of cell death (preferably by apoptosis). We hypothesize that inducing programmed cell death in the prostate will reduce the risk of developing cancer later on.

We have chosen a transgenic mouse model for of prostate cancer (transgenic adenocarcinoma of the mouse prostate, "TRAMP", ref. 6) to perform the targeting of a pro-apoptotic moiety to the prostate vasculature. In this system, a prostate specific promoter from the rat probasin gene has been used to cause the expression of T antigen specifi-

cally in the prostate. These mice develop prostate tumors through temporally and histologically distinct stages, similarly to what happens in the human disease. Pathologic alterations in the prostate epithelium of these mice are seen by 10 weeks of age, and metastases may develop at 12 weeks. By week 28, all animals harbor metastatic prostate cancer in a pattern resembling the human disease (6). We have an established colony of these mice at our Animal Facility. Prior to treatment, we will establish cohorts of 30 age-matched male TRAMP mice by cross-breeding female TRAMP x male Fab mice. This F1 generation with a 50% Fab background presents an aggressive disease (B. Foster and N. Greenberg, personal communication). The cohorts will be randomized in 3 treatment groups: prostate-homing peptide alone, prostate targeted pro-apoptotic peptide, and pro-apoptotic peptide conjugated to a control peptide. In selected cases, a vehicle-only treatment group will be included as an additional control for comparison. However, our preliminary results suggest that the prostate-homing peptide SMSIARL alone has no effect on the prostate at the concentrations used.

It has been suggested that anti-angiogenic therapy is more efficient whether it is delivered at low doses for a long duration (18). If this is the case, we expect that our results may become even better when the optimal dose/schedule are determined. For the pilot experiments shown here, we have been treating the mice at a single dose near the maximum tolerated dose (MTD; data not shown). Thus, we will start treatments at 20 µg /dose/mouse and escalate dosing. Treatments will be administered weekly (IV). We will initiate treatment cohorts at 10 and 12 weeks of age. Further dose, timing, and route adjustments will be based on data from these experiments. Mice will be anesthetized with Avertin® to facilitate IV injections. The efficacy of targeted and control compounds on tumor growth, metastasis and their associated toxicity will be plotted as survival of the cohorts using Kaplan-Meier curves. For each compound, we will determine median survival, and percentage increase in life span [%ILS=(T-C)/Cx100, where T=treated and C=control]. We expect to see an increase in the median survival and %ILS; with a reciprocal decrease in metastasis in the targeted pro-apoptotic peptide groups relative to controls. We will also euthanize the mice at fixed intervals (e.g., 15, 20, 25, and 30 weeks) and evaluate the primary tumor and metastatic burden. Moreover, we will mate the treated mice (transgenic and normal) to assess their fertility.

This research makes use of two new principles: Targeting of tissue-specific features in the prostate vasculature and induction of organ-directed apoptosis. We will determine in mice prone to develop prostate cancer whether reducing prostatic mass protects against cancer development. New understanding of prostate biology may ensue: transfer of our findings into clinical application has the potential to provide novel medical tools against human prostate cancer.

D. REFERENCES

1. Arap W, Pasqualini R, and Ruoslahti E. Chemotherapy targeted to tumor vasculature. *Curr Opin Oncol*, in press.

2. Arap W, Pasqualini R, and Ruoslahti E. Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model. *Science* 279:377-380, 1998.

3. Burg MA, Pasqualini R, Arap W, Stallcup WB, and Ruoslahti E. Identification of NG2 proteoglycan-binding peptides that home to tumor neovasculature. In preparation.

4. Cox AL, Skipper J, Chen Y, Henderson RA, Darrow TL, Shabanowitz J, Engelhard VH, Hunt DF, and Slingluff CL Jr. Identification of a peptide recognized by five melanoma-specific human cytotoxic T cell lines. *Science* 264:716-719, 1994.

5. Folkman J. Is tissue mass regulated by vascular endothelial cells? Prostate as first evidence. *Endocrinology* 139:441-442, 1998.

6. Gingrich JR, Barrios R, Morton RA, Boyce B, Mayo F, Finegold MJ, Angelopoulou R, Rosen JM, and Greenberg NM. Metastatic prostate cancer in a transgenic mouse. *Cancer Res* 56, 4096-4102, 1996.

7. Hart SL, Knight AM, Harbottle RP, Mistry A, Hunger HD, Cutler DF, Williamson R, and Coutelle C. Cell binding and internalization by filamentous phage displaying a cyclic Arg-Gly-Asp-containing peptide. *J Biol Chem* 269:12468-12474, 1994.

8. Javadpour MM, Juban MM, Lo WC, Bishop SM, Alberty JB, Cowell SM, Becker CL, and McLaughlin ML. De novo antimicrobial peptides with low mammalian cell toxicity. *J Med Chem* 39:3107-3113, 1996.

9. Kawakami Y, Eliyahu S, Delgado CH, Robbins PF, Sakaguchi K, Appella E, Yannelli JR, Adema GJ, Miki T, and Rosenberg SA. Identification of a human melanoma antigen recognized by tumor-infiltrating lymphocytes associated with in vivo tumor rejection. *Proc Natl Acad Sci* 91:6458-6462, 1994.

10. Mandelboim O, Berke G, Fridkin M, Feldman M, Eisenstein M, and Eisenbach L. CTL induction by a tumour-associated antigen octapeptide derived from a murine lung carcinoma. *Nature* 369:67-71, 1994.

11. Pasqualini R, Arap W, Rajotte D, and Ruoslahti E. In vivo phage display. In: Phage display. C Barbas, J Scott, and G Silvermann (eds.), Cold Spring Harbor Press, Cold Spring Harbor, New York, in press.

12. Pasqualini R, Koivunen E, and Ruoslahti E. αv integrins as receptors for tumor targeting by circulating ligands. *Nature Biotechnol* 15:542-546, 1997.

13. Pasqualini R and Ruoslahti E. Organ targeting in vivo using phage display peptide libraries. *Nature* 380:364-366, 1996.

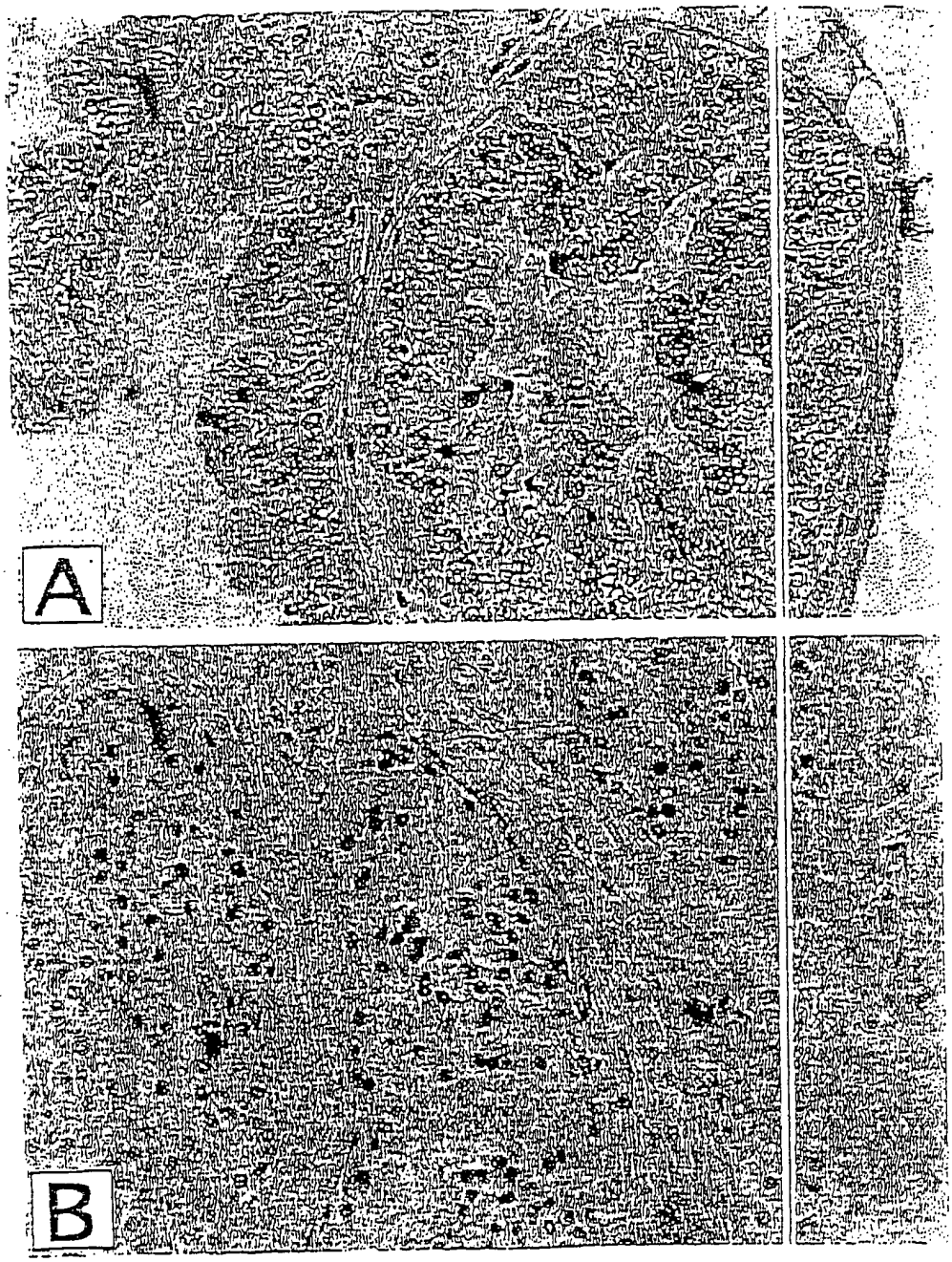
14. Rajotte D, Arap W, Hagedorn M, Koivunen E, Pasqualini R, and Ruoslahti E. Molecular heterogeneity of the vascular endothelium revealed by in vivo phage display. *J Clin Invest* 102:430-437, 1998.

15. Resnicoff M, Huang Z, Herbst D, Abraham D, and Baserga R. A novel class of peptides that induce apoptosis and abrogate tumorigenesis in vivo. *Biochem Biophys Res Comm* 240:208-212, 1997.

16. Smith GP and Scott JK. Libraries of peptides displayed in filamentous phage. *Meth Enzymol* 217:228-257, 1993.

17. Vitetta ES, Krolick KA, Miyama-Inaba M, Cushley W, and Uhr JW. Immunotoxins: A new approach to cancer therapy. Science 219:644-650, 1983.

18. Zetter B. Tumor angiogenesis and metastasis. *Ann Rev Med* 49:407-427, 1998.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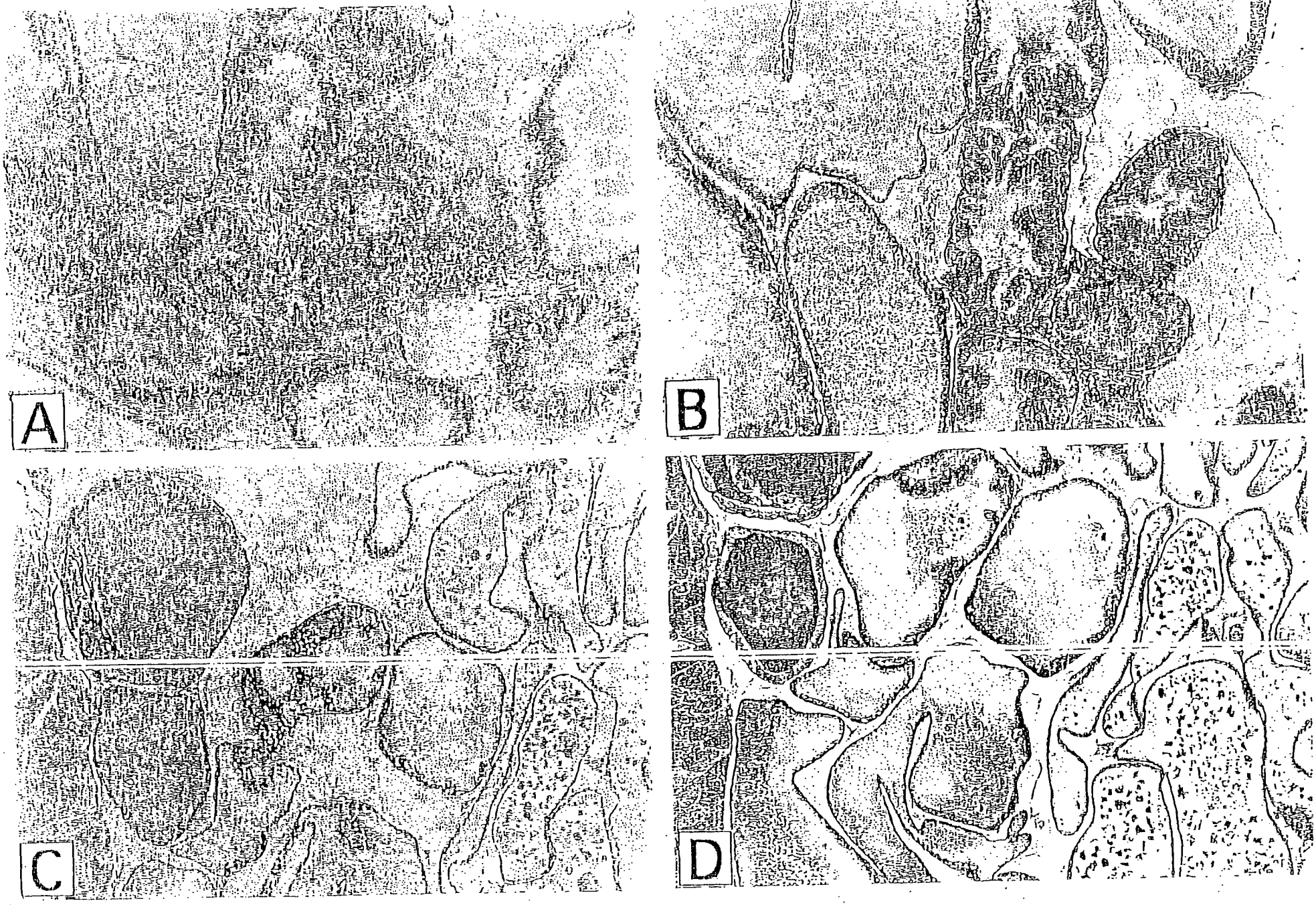
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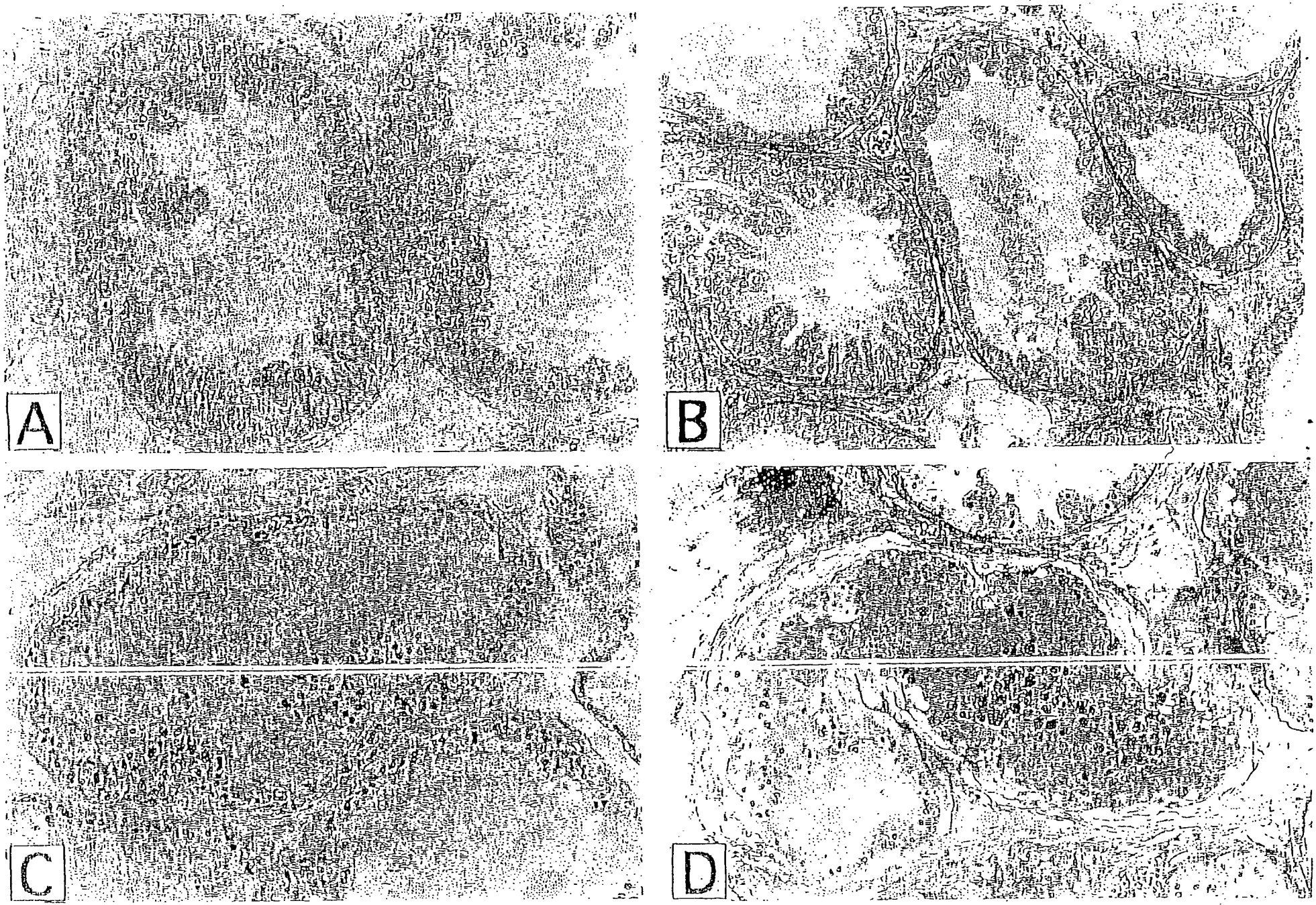
A
B
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A

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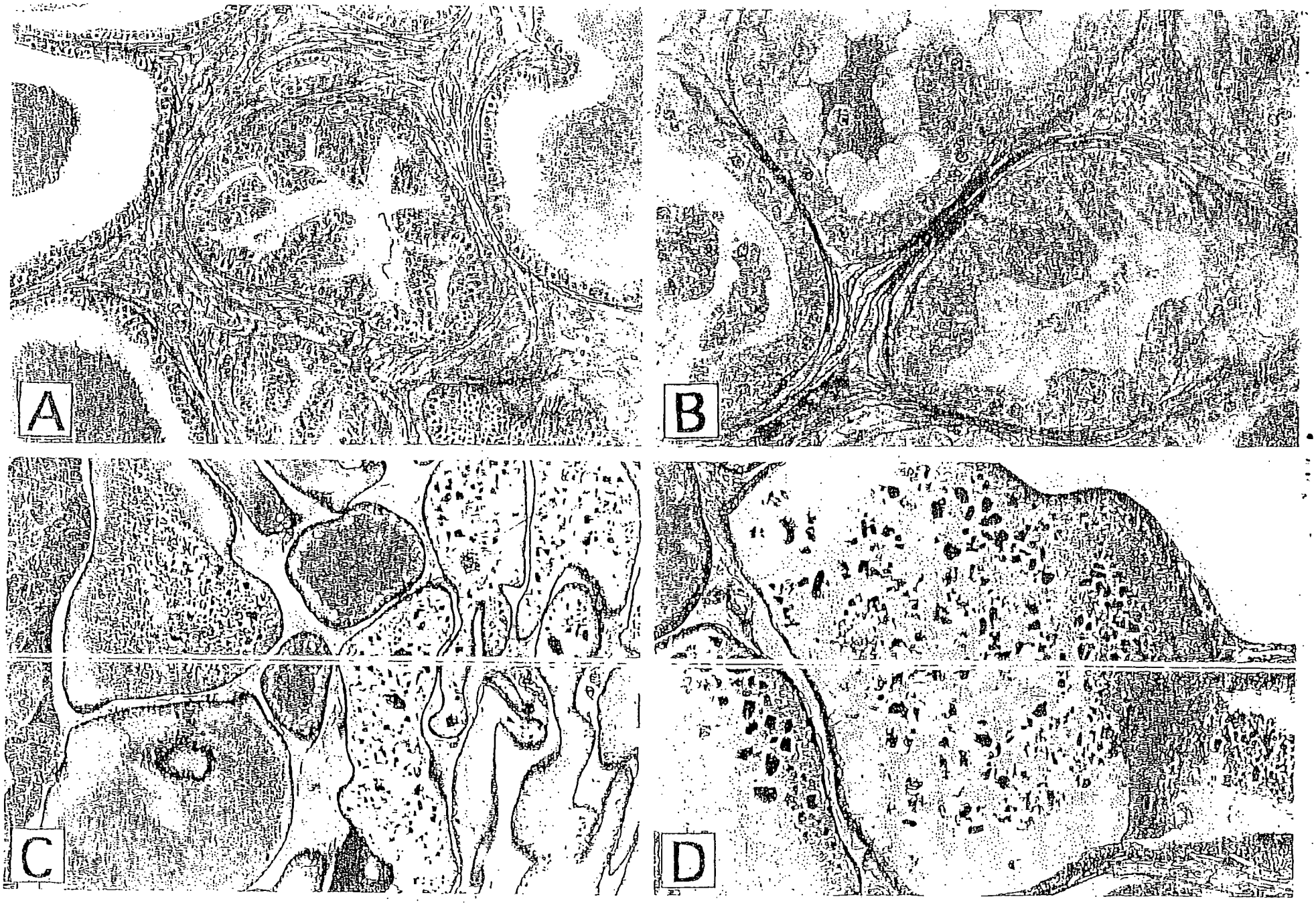
A
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